Chapter 3

Simple and Facile Benzylic C-H Oxidation Using (Diacetoxyiodo)benzene and Catalytic Sodium Azide
Abstract

A convenient and capable Benzylic C-H Oxidation of alkyl and cycloalkyl arenes using (diacetoxyiodo) benzene and catalytic amount of NaN$_3$ in aqueous acetonitrile is described. This is a simple synthetic utility of hypervalent iodine reagent (diacetoxyiodo) benzene; with a catalytic amount of sodium azide for benzylic C-H oxidation of alkyl and cycloalkyl arenes in aqueous acetonitrile solvent system gave corresponding benzylic ketones (78-89%). Advantages of this system are short reaction time, easy work-up, mild reaction conditions and good yields.

3.1 Introduction:

C-H bond transformation is capable and sustainable requirement of organic transformations. It also has some fundamental features in organic molecules for example, their convenience, activity and selectivity (Dyker, 2005; Labinger et al., 2002; Jones et al., 1989; Bergman et al., 2007). C-H bond activation is one of the most Common processes in nature. Transition metals having high abilities for C-H oxidation by SET (single electron transfer) process (Fridovich, 1978; Han et al., 1995., Roach et al., 1997; Ford et al., 2005). The oxidation of activated benzylic C-H bonds is of basic importance in the large scale synthesis of specialty chemicals, (Sheldon et al., 1981) the costly late transition metals like Pt, Rh, Ir Pd, play key roles to make easy highly efficient transformations through C-H activation (Lersch et al., 2005; Yang et al., 2009; Rtleng et al., 2002; Colby et al., 2010; Cho et al., 2002; Mkhalid et al., 2010; Conejero et al., 2010; Jia et al., 2000; Lyons et al., 2010; Chen et al., 2009; Shilov et al., 1997).
These reactions required oxidants like potassium permanganate or potassium dichromate (Rangarajan et al., 1985; Pearson, et al., 1985; Choudary et al., 1992, Gannon et al., 1987; Zhao et al., 1994; Pan et al., 2001). The metal complexes like Ru, Mn, Fe, Rh, Zn and Cr are also used for the of the transformations (Murahashi et al., 2000; Lee et al., 1998; Kim et al., 2002; Catino et al., 2004; Gupta et al., 2005; Muzart et al., 1991, 9186; 1987). The main disadvantages of the use of such reagents are their toxicity, the charge of waste removal and the removal of residual metal from the aromatic product (Banik et al., 1998) reported the use of sodium bismuthate for benzylic oxidation reactions, but the major problem of this process is the poor solubility of the bismuthate and long reaction time (Salvador et al., 2005). In result, the intensification of a benzylic oxidation reaction with a readily available and economical reagent of low toxicity would be of considerable importance.

3.2 Literature Survey:

The direct benzylic oxidation of alkylarenes is an important protocol to offer the corresponding carbonyl compounds for employ as versatile building blocks in the construction of functional chemicals and pharmaceuticals. There are many methods available for direct benzylic oxidation of alkylarenes using alkylarenes as starting materials.

3.2.1 The direct benzylic oxidation of alkylarenes:

This includes either using hypervalent iodine reagents or others.

a) Polymeric Iodosobenzene with KBr:

They have found that polymeric Iodosobenzene [PhIO]n induced aqueous benzylic C-H oxidation to successfully give arylketones, in the presence of KBr and Montmorillonite-K10 (M-K10) clay (Kita et al, 2008). Water-soluble and reactive species having the unique I (III)-Br bond, in situ generated from [PhIO]n and KBr was considered to be the key radical initiator during the reactions.
This methodology having mainly 2–3 drawbacks that are, required reaction time is more than 24 hrs and most of substrates having low yield of reaction.

b) Using permanganate adsorbed on a solid support.

Alkylbenzenes side chain is oxidized at the benzylic position when reacted under heterogeneous conditions (Zhao et al., 1997).

With permanganate adsorbed on a solid support, the oxidation of derivatives of indane and tetralin in which one of the methylene under goes oxidation to formed ketones using KMnO₄/CuSO₄.H₂O reaction system. This reaction system required 70-120 hrs for the completion of reaction. There are very few substrates under goes this transformation to obtained equivalent product.
c) Chromium-Pillared Clay as a Catalyst.

Benzylic oxidation of arylmethylenes to the related carbonyl compounds is described using catalytic amount of Chromium-pillared montmorillonite and equimolar quantities of tert-butyl hydroperoxide (Chaudhary et al., 1992).

![Scheme 3.4]

In this reaction oxidation of the benzylic methylene group was carried out at ambient temperature in dry CH₂Cl₂ containing a catalytic amount of chromium-pillared clay catalyst and 2 equiv of TBHP for 36-50 h giving the corresponding ketones. This reaction system also having major drawback i.e. required reaction time is very high about 36-50 hrs and limited substrates under goes this conversion to formed desired product.

d) Benzylic Oxidation by Sodium Bismuthate in Acetic Acid.

![Scheme 3.5]
Oxidation of benzylic methylenes in polycyclic systems to the benzylic ketones was carried out with sodium bismuthate in the presence of acetic acid. (Becker et al., 1998) few substrates can be converted to corresponding ketones.

e) 2-Quinoxalinol Salen Copper Complexes:

A copper (II) complex of the 2-quinoxalinol salen ligand (salquCu) (A) has been experienced for use in catalysis (Garden Anne et al., 2009).

\[
\text{Catalyst (A)} = \text{(salquCu)}
\]

\[
\text{CH}_3\text{CN, Reflux, 18 hrs, tBuOOH in decane}
\]

Where \( R = \text{alkyl, aryl, ether, ester etc.} \)

\[
\text{Scheme 3.6}
\]

In above reaction system hazardous reaction conditions are used, also reaction takes place at reflux temperature up to 18 hrs. Indane, fluorine, xanthenes, anthracene does not undergo this transformation with the help of this reaction system.

f) \( \text{NaBrO}_3 \) in the presence of \( \text{NH}_4\text{Cl} \) or \( \text{Bu}_4\text{NHSO}_4 \)

In this methodology Alkylbenzenes are oxidized selectively to their carbonyl compounds by sodium bromate in the presence of \( \text{NH}_4\text{Cl} \) or \( \text{Bu}_4\text{NHSO}_4 \).

\[
\text{NaBrO}_3 / \text{Bu}_4\text{NHSO}_4 \quad \text{CH}_3\text{CN} / \text{H}_2\text{O}
\]

Where \( R = \text{alkyl, aryl etc.} \)

\[
\text{Scheme 3.7}
\]
They have observed that NaBrO$_3$/Bu$_4$NHSO$_4$ is a more capable oxidizing agent than NaBrO$_3$/NH$_4$Cl for the translation of alkylbenzenes to aldehydes and ketones. Oxidation of benzylic methylenes in polycyclic systems to the benzylic ketones was not respond for this reaction system so, this is drawback of this methodology and reaction time for this conversion is also high (8 to 24 hrs).

**g) Organoselenium Catalyst and TBHP**

Benzisoselenazol-3(2H)-one covalently bounded to a silica support was synthesized and characterized. It was used as catalyst for t-BuOOH and H$_2$O$_2$ oxidation of alkyl arenes to alkyl aryl ketones (Młochowski et al., 2008).

![Scheme 3.8](image)

Where R = alkyl, aryl etc.

HELICAT = cyclic selenenamide moiety bounded to a solid silica support by a propylene group

Benzylic methylenes in polycyclic systems do not under goes these transformations to form the benzylic ketones.

**h) Bismuth-Catalyzed Benzylic Oxidations with tert-Butyl Hydroperoxide**

Oxidation of alkyl and cycloalkyl arenes with tert-butyl hydroperoxide catalyzed by bismuth and picolinic acid in pyridine and acetic acid gave the resultant benzylic ketones (Barrett et al., 2005).
I) Copper (II)-catalyzed C-H oxidation:

Copper (II) complex (A) capably catalyses the oxidation of alkylbenzenes and cyclohexane into the corresponding ketones in moderate to high yields in the presence of 30% H$_2$O$_2$ (Punniyamurthy et al., 2003).

This reaction system required high time to converts starting material to product and limited substrates under goes this transformation to obtained wanted products.

j) Using Chloramine-T/O$_2$/Fe (TPP) Cl system:

The Fe complex of meso-tetrakisphenyl porphyrin (TPP) was used as the catalyst in the presence of Chloramine-T for the oxidation of hydrocarbons to the corresponding ketones (Wang et al., 2005).
Reaction required 24 hrs.
3.3 Objectives and Scope

The present work was undertaken for the exploration of reaction between activated carbon and DIB and catalytic amount of NaN₃ as source of oxidant. This idea develops a new methodology having wide application in organic synthesis.

3.4 Work done on each objective

Our research group is widely working on the hypervalent iodine reagents mediated new methodology development. Particularly Trivalent iodine reagents i.e. DIB, (Dichloroiodo) arenes, PIFA mediated methodologies, these are found very much applicable in organic synthesis. DIB in combination with NaN₃ in aqueous acetonitrile, a system developed in our lab, found a good source of oxidative reagent (Fig 3.1) DIB and NaN₃ Complex.

![Fig 3.1](image)

This combination is used to expand variety of transformations like synthesis of benzyol azide from benzaldehyde (Chen et al., 2000) cinnamic acid to vinyl azide, oxidative decarboxylation of phenyl acetic acid, (Telvekar et al., 2009; 2010) electrophilic aromatic azidation (Kita et al., 1994). Direct azidation of acetyl acetone like 1, 3 diketones (Lee, J. C et al., 2000) Synthesis of vicinal diazides, (Chang, 2004) addition to olefinic compounds, azidation of ethers (Bols et al., 2005)
With these reactions as background, herein we report the extension of this chemistry. We subjected Diphenylmethane to react with DIB and catalytic amount of NaN₃ Combination to get direct benzylic oxidation of alkylarenes via C-H bond abstraction (see Scheme 3.1).
3.4.1 Plausible mechanism for the above transformation has been given as shown in (Fig 3.3).

(Diacetoxyiodo) benzene react with NaN₃ formed species (A) by ligand exchange followed by Homolytic decomposition to generate an azido radical. Which abstract proton from active methylene group to form methylene radical which undergoes azide addition and this adduct further hydrolyse to form ketone as final product. The direct C-H bond functionalization of hydrocarbons via C-H bond activation for organic synthesis has fascinated much attention in recent years. In particular, chemoselective functionalization under metal-free conditions, which is one of the requirements for the realization of green chemical processes, remains a great challenge in organic chemistry. As a representative C-H bond functionalization process, the direct benzylic oxidation of alkylarenes is an important protocol to provide the corresponding carbonyl compounds for use as versatile building blocks in the production of functional chemicals and pharmaceuticals. As part to develop new methodology, DIB and NaN₃ combination was reacted with substrate to achieve expectedly desired ketones.
3.5 Results and Discussion

In our preliminary experiments 1.0 equivalent of diphenyl methane was treated with 2 equivalents of DIB in combination with catalytic amount of NaN₃ in aqueous acetonitrile at room temperature, as expected benzophenone was obtained in excellent yields in 25 min. Completion of the reaction was monitored by Thin Layer chromatography (TLC). After completion of reaction workup carried out as given in experimental procedure, pure product was isolated by column chromatography.

Product obtained was characterized with the physical and spectral properties and compared with authentic sample. It was confirmed that benzophenone is the product.

![Benzophenone](image)

White solid, mp 47-48 °C (lit.19 mp 47.5 °C), ¹H NMR (300 MHz, CDCl₃): δ 7.80-7.78 (d, J = 7.8Hz, 4H), 7.59-7.54 (t, J = 7.35Hz, 2H) 7.49-7.44 (t, J = 7.5Hz, 4H) ppm. IR (KBr) vmax: 3060, 3030 and 1659 cm⁻¹.

To begin exhaustive study for the transformation, we have chosen Diphenyl methane as model substrate to optimize reaction conditions and substrate study for the generalization of conversion with chemo selectivity.

a. Solvent study
b. Temperature and reaction time
c. Reagent mole ratio
d. Generality of the substrates
a. Solvent study:

After successful formation of benzophenone, consistency of reaction conditions with respect to solvent was carried out and the results are summarized in Table 3.1

**Table 3.1: Solvent study for Diphenyl methane to benzophenone**

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Solvent</th>
<th>Substrate (mmol)</th>
<th>Time (min)</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MDC</td>
<td>1</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>Acetone:H₂O</td>
<td>1</td>
<td>25</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CN:H₂O</td>
<td>1</td>
<td>25</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN</td>
<td>1</td>
<td>25</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>Water</td>
<td>1</td>
<td>25</td>
<td>78</td>
</tr>
</tbody>
</table>

*aReaction conditions: substrate (5.91 mmol), (diacetoxyiodo)benzene (2 equiv), and NaN₃ (0.1 equiv) in CH₃CN:H₂O (10 mL). bIsolated yields after column chromatography

Aqueous acetonitrile was found to be good solvent for this transformation (Table 3.1, entry 3). In case of solvents like MDC, CH₃CN, aqueous Acetone shows reaction was slow and gave lower yields (Table 3.1, entries 1, 4 & 2). In case of Water, reaction gave better results with respect to yield than the other solvents (Table 3.1, entries 5). Aqueous acetonitrile become a solvent of choice due to smooth reaction and high yields.
b. Reaction Time and Temperature:

Optimization of reaction condition in terms of time and temperature is also carried out and results are shown in (Table 3.2). Reactions were carried out at different temperatures from room temperature to reflux but, it was observed that at room temperature reaction takes place efficiently smooth, clean and gives good yields. In case of Diphenylmethane reaction was completed in 25 min. and no further reaction was observed even after continuing the reaction for 24 h. However in case of aliphatic substrates, reaction does not take place even reaction kept up to 72 hrs.

Table 3.2 Reaction Time and Temperature study for Diphenylmethane to benzophenone:

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Reagent Con.</th>
<th>Temperature</th>
<th>Time(Min)</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIB (2 equiv):Cat.NaN₃</td>
<td>r.t</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>DIB (2 equiv):Cat.NaN₃</td>
<td>r.t</td>
<td>10</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>DIB (2 equiv):Cat.NaN₃</td>
<td>r.t</td>
<td>15</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>DIB (2 equiv):Cat.NaN₃</td>
<td>r.t</td>
<td>25</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>DIB (2 equiv):Cat.NaN₃</td>
<td>r.t</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>DIB (2 equiv):Cat.NaN₃</td>
<td>r.t</td>
<td>120</td>
<td>87</td>
</tr>
</tbody>
</table>

The reaction was studied at different time intervals, a reaction time from 5 min up to 25 min the yield of product obtained is increases. We found that 25 min were required for conversion.

c. Reagent Mole Ratio:

Initially, the reaction was carried out by using 0.5 mmol of DIB and Catalytic NaN₃, which provided desired product in 30% yields. An increase in the DIB concentration up to 2 mmol resulted in an increase in the yield of 87% (Table 3.3, entry 3). Further increase in the amount of DIB (more than 2mmol) had no profound effect on the yield of the desired product (Table 3.3, entry 4). Also, the reaction was carried out at
different NaN$_3$ concentration ranging from 0.05 mmol to 1 mmol. It was observed that only Catalytic NaN$_3$ is 0.1 equiv is sufficient for completion of reaction. However, a further increase in concentration did not show any significant enhancement in the yield (Table 3.3, entry 4).

**Table 3.3 Reagent moles study Diphenylmethane to benzophenone**

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Reagent Ratio</th>
<th>Substrate</th>
<th>Time</th>
<th>Yield$^b$%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 : 0.1</td>
<td>1</td>
<td>25</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>1.5 : 0.1</td>
<td>1</td>
<td>25</td>
<td>77</td>
</tr>
<tr>
<td>3$^a$</td>
<td>2 : 0.1</td>
<td>1</td>
<td>25</td>
<td>87</td>
</tr>
<tr>
<td>4$^c$</td>
<td>2.5 : 0.1</td>
<td>1</td>
<td>25</td>
<td>87</td>
</tr>
</tbody>
</table>

$^a$ Reactions were conducted on 2 mmol scale, $^b$ By Gas Chromatography, $^c$ No more conversion even after increasing reaction time.

3.5.1 Optimized Reaction Condition:

With these studies, it is noted that most excellent results were obtained with 2 equiv of DIB and 0.1 equiv NaN$_3$ in aqueous acetonitrile at r.t. (Table 3.3, entry 3) and all further reactions were carried out using these optimized parameters.

e. Generality of the Substrates

With these results in hand to explore the reaction scope, a variety of benzylic, alkyl and cycloalkyl arenes compounds were subjected to this reaction condition and oxidized to the corresponding ketones in moderate to good yields; the results are summarized in (Table 3.4)
Table 3.4: Substrate study for direct C-H bond functionalization of hydrocarbons and polycyclic compounds to corresponding ketones$^a$

<table>
<thead>
<tr>
<th>Sr.No</th>
<th>Substrate</th>
<th>Product</th>
<th>Time (Min)</th>
<th>Yield$^b$%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="substrate1.png" alt="" /></td>
<td>![product1.png]</td>
<td>20</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td><img src="substrate2.png" alt="" /></td>
<td>![product2.png]</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td><img src="substrate3.png" alt="" /></td>
<td>![product3.png]</td>
<td>20</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td><img src="substrate4.png" alt="" /></td>
<td>![product4.png]</td>
<td>20</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td><img src="substrate5.png" alt="" /></td>
<td>![product5.png]</td>
<td>25</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td><img src="substrate6.png" alt="" /></td>
<td>![product6.png]</td>
<td>25</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td><img src="substrate7.png" alt="" /></td>
<td>![product7.png]</td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>No</td>
<td>Substrate</td>
<td>Product</td>
<td>Reaction Temperature</td>
<td>Isolated Yield</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>---------</td>
<td>----------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>8b</td>
<td><img src="image" alt="Substrate 8" /></td>
<td><img src="image" alt="Product 8" /></td>
<td>30</td>
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</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Substrate 9" /></td>
<td><img src="image" alt="Product 9" /></td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Substrate 10" /></td>
<td><img src="image" alt="Product 10" /></td>
<td>30</td>
<td>85</td>
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<td><img src="image" alt="Substrate 11" /></td>
<td><img src="image" alt="Product 11" /></td>
<td>30</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Substrate 12" /></td>
<td><img src="image" alt="Product 12" /></td>
<td>25</td>
<td>80</td>
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<td>13</td>
<td><img src="image" alt="Substrate 13" /></td>
<td>------</td>
<td>120</td>
<td>NR&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reaction conditions: substrate (5.91 mmol), (diacetoxyiodo)benzene (2 equiv), and NaN₃ (0.1 equiv) in CH₃CN:H₂O (10 mL). <sup>b</sup>Isolated yields after column chromatography and structures were confirmed by comparison of IR and ¹H NMR with authentic materials. <sup>c</sup>No reaction.

To explore simplification of the reaction, range of substrates were reacted with optimized reaction condition i.e. 2.0 equivalents of DIB in combination with 0.1 equivalent of NaN₃ at room temperature in aqueous acetonitrile and results are summarized in (Table 3.4)
To expand the scope of our reaction system Diphenylmethane subjected to C-H activation reaction, in this case we were found to respond smoothly providing highest yield of benzophenone as preferred product. It is noteworthy to mention that no other by-product in case of DPM (diphenyl methane) was obtained. We also checked the role NaN₃ in our reaction System. In the presence of catalytic NaN₃ in the reaction system we got desired product with very good yield.

To explore the simplification and applicability of the protocol, we turned our attention towards the direct benzylic oxidation of polycyclic compounds via C-H bond abstraction with DIB (2equiv) and catalytic NaN₃. The reaction gave 80-85% yield of corresponding ketones under the optimized reaction conditions, however in the absence of NaN₃, the yield obtained tiny. Thus, the developed protocol proved to be general for the direct benzylic oxidation of alkylarenes via C-H bond abstraction DIB (2equiv), NaN₃ (0.1equiv) and aqueous acetonitrile providing good to excellent yield of the desired product We think that the presence of NaN₃ plays the role of catalyst, the effect of various solvents on benzylic oxidation of alkylarenes was studied to find out the Acetonitrile: water solvent system provides good yields. During optimization of the reaction parameters, it was found that five- and six member cyclic compounds successfully undergo oxidation reaction indane and tetralin afforded the corresponding ketones compounds in good yields (Table 3.4, entries 2–5). In case of polycyclic compounds like 9H-flurene we got corresponding fluorinone product with good yield (Table 3.4, entry 2).

In case of Heterocyclic compounds such as 9H-xanthene also converted into corresponding 9H-xanthen-9-ones (Table 3.4, entry 5). The developed method is also applicable for the preparation of anthacene-9, 10-dione (Table 3.4, entry 12) with good yield using DIB (2 equiv) and NaN₃ (0.1 equiv) in acetonitrile: water reaction system at room temperature. In order to study the promising and general applicability of the developed methodology, various alkylarenes containing different polycyclic rings were subjected to this transformation. We observed that five members, six member and other polycyclic compounds provided significant yield of products. Further investigations indicated that linear alkylbenzenes also are suitable compounds for this transformation; 1-ethynaphthalene, ethyl benzene, (2-methylpropyl) -benzene and propylbenzene successfully converted to corresponding ketones in a short reaction time (Table 3.4, entries 7–10). Under these reaction conditions, no
hydrolysis of ether and ester groups was observed (Table 3.4, entries 10 and 11). It was interesting to know that only benzylic compounds undergo this reaction transformation, and thus no reaction was observed when toluene was subjected to these reaction conditions (Table 3.4, entry 13). All the ketones were characterized by comparing spectral properties and comparing their physical properties with that of reported compounds in the literature. Detail data is presented in the experimental section. All the ketones showed characteristic C=O stretching peak at 1685-1695.
$^1$H NMR Spectra of Benzophenone (Table 3.4, Entry 1)
IR Spectra of Benzophenone (Table 3.1, Entry 1)
\(^1\text{H NMR Spectra of 3, 4-dihydronaphthalen-1(2H)-one (Table 3.1, Entry 3)}\)
IR Spectra of 3, 4-dihyronaphthalen-1(2H)-one (Table 3.1, Entry 3)
3.6 Mechanism for the transformation:

To explore the mechanism of this transformation, there is require introducing the reported reaction i.e. reaction of polymeric Iodosobenzene [PhIO] n and catalytic KBr in (Scheme 3.2). In this reaction polymeric Iodobenzene and KBr make a complex reagent which is responsible for this transformation and plays a vital role to proceed the reaction to form benzyl radical like intermediate, which under goes α- bromination further on hydrolysis and oxidation of that product got ketones as product. This benzyl radical intermediate formation is the key step to get respective product. We have represented plausible mechanism for the transformation in (Scheme 3.2)

In particular, we have previously found that the activation of the (Diacetoxyiodo) benzene by sodium azide in aqueous acetonitrile is a successful method for the useful and unprecedented hypervalent iodine (III)-induced oxidative decarboxylation reaction of phenyl acetic acid to benzaldehydes. Detailed studies on the mechanism shown that the reaction involves the generation of a water-soluble species (1) having the unique I (III)-N₃ bond as a reactive intermediate. On the basis of a previous report and unique reactivity of hypervalent iodine (III) – azide bonds for initiating radical reactions, we assumed that the reaction of (1) in water is the development of a new aqueous benzylic oxidation via the radical pathway (fig 3.4).

**Fig 3.4: Radical Formation from (1) via Homolytic Cleavage of the Labile I (III)-N₃ Bond in aqueous acetonitrile solvent:**

![Fig 3.4](image-url)
A plausible description for the reaction mechanism is exemplified by the conversion of ethyl benzene (Scheme 3.12). First, as we formerly confirmed (Diacetoxyiodo) benzene and NaN₃ was react in aqueous acetonitrile and generated reactive species (A). The reactive (A) could produce the iodanyl radical (Scheme 3.12) by facile Homolytic cleavage of the labile I(III)-N₃ bond, initiating the radical reaction with ethyl benzene. Thus, selective abstraction of the benzylic hydrogen atom in ethyl benzene by the iodine-centered radical (A) would create the resultant benzyl radical. The resulting benzyl radical was probably trapped by the persistent azide radical in situ giving rise to the stable benzyl azide intermediate. The conversion of the benzyl azide intermediate to the alcohol and subsequent oxidation of secondary alcohol by the second molecule of the oxidant would finish the series of benzylic oxidation processes to afford the observed arylketones.

**Proposed Reaction Mechanism for conversion for above conversion**

**3.7 Suggested Potential Applications of Methodology:**

This process could be useful in the synthesis of bioactive molecules, for example: Ambrisentan, Chlorphenoxamine, delucemine, donepezil, fedolmidine specific juvenile harmone mimic is synthesized with the route having ketone introduction step as shown in
A) Donepezil

Its main therapeutic use is in the palliative treatment of mild to moderate Alzheimer's disease. Alzheimer disease, is the most common form of dementia. Dementia is not a single disease, but rather a non-specific illness Syndrome.

![Scheme 3.13]

b) Fedolmidine

Fadolmidine (MPV-2426) is a novel α2-adrenoceptor (α2-AR) agonist developed for spinal analgesia. Fadolmidine has been effective against various submodalities of pain such as heat pain, mechanical pain, and visceral pain. In general, the antinociceptive potency of fadolmidine, i.t. was equal to that of dexmedetomidine.
3.8 Summary & Conclusion:

In conclusion, we have developed a protocol for direct benzylic oxidation of alkylarenes via benzylic C-H abstraction using the diacetoxyiodo benzene and catalytic sodium azide without heavy metals. This selective oxidation significantly shows that it proceeds through photooxidation depending on the Substituents of the alkylarenes to give corresponding carbonyl compounds. This method is an environmental sustainability approach for organic synthesis as it does not involve heavy metals and use organic reagents under mild conditions. In general, all kinds of functional groups were very well tolerated giving higher yields. This method exhibits a broad scope, affords spotless product in moderate to high yields and will be of immense efficacy in organic synthesis. Lower reaction time adds an additional credit to the present study. In general, all kinds of benzylic C-H activated groups were very well under goes this transformation giving higher yields. The reaction was optimized with respect to various reaction parameters and enabled direct benzylic oxidation of alkylarenes via C-H bond and polycyclic compounds C-H bind abstraction was developed, affording excellent yields of the desired products, thus illustrating the broad applicability of the methodology. The developed protocol might prove a hopeful alternative for synthesis of aryl or polycyclic ketones using (diacetoxyiodo) benzene and catalytic azide which generate reactive species in situ which is
responsible for this organic transformation. In summary, an efficient and mild method for the conversion benzylic C-H activated groups were very well under goes this transformation to corresponding ketones with Hypervalent iodine reagent like DIB and NaN$_3$ in aqueous acetonitrile at room temperature.

3.9 Experimental Section:

3.9.1 Preparation of (Diacetoxyiodo) benzene i.e. DIB

A) Optimized Procedure for Preparing (Diacetoxyiodo) arenes from Iodoarenes:

Urea-Hydrogen Peroxide adduct, 98% (3.02 g, 31.5 mmol, 350% excess) was added portion wise to a stirred mixture of glacial AcOH (24 mL) with Ac$_2$O (9 mL). An appropriate iodoarene (7 mmol) was slowly added; the solution was cooled to 10-15 °C, and powdered AcONa (1.26 g, 15 mmol) was suspended. Stirring at 40 °C was continued for 3.5 h. After cooling, water (35 mL) was slowly added with stirring. The precipitated ArI (OAc)$_2$ were collected by filtration, washed on the filter with a cold (5-10 °C) 10% aq. AcOH, and air-dried in the dark; if necessary, they were recrystallized from AcOEt/AC$_2$O (9:1, v/v). The oily or semisolid products were extracted with CH$_2$Cl$_2$, the combined extracts were dried over anhydrous Na$_2$SO$_4$ and filtered, the solvent was distilled off under vacuum, and the solidified residues were recrystallized from AcOEt/AC$_2$O (9:1). The purities and homogeneities of the purified ArI (OAc)$_2$ were firstly checked by TLC, and next confirmed by their melting points, all close to those reported in the literature. Their chemical structures were fully supported by the $^1$H- NMR and $^{13}$C-NMR, spectra (in CDCl$_3$) (Skulski.L et al., 2005, 2002).

3.9.2 General experimental procedure for benzylic oxidation of alkylarenes or polycyclic alkylarenes via C-H bond abstraction to ketones (Table 2.4, entry 1)

Catalytic NaN$_3$ (0.1 equiv) was added to a stirred solution of (diacetoxyiodo) benzene (2 equiv) in CH$_3$CN: H$_2$O (10mL) at room temperature. The reaction mixture was stirred for 2 min, followed by addition of diphenylmethane (1.0 equiv, 5.91 mmol). After completion of the reaction (thin-layer chromatography, TLC), the reaction mixture was diluted with H$_2$O (25 mL) and the resultant solution was extracted with CH$_3$Cl (2x25 mL). The combine organic layer was washed successively with 10%
sodium bisulfate solution (2x20 mL), 10% sodium bicarbonate (2x15 mL), and water (2x20 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product. Pure diphenylmethanone (85%) was obtained after silica-gel column chromatography (10% EtOAc-hexane).

3.10 Characterization Data of Ketones

IR and NMR data were identical with those of authentic sample and data are given below

Benzophenone (Table 3.4, Entry 1)

![Benzophenone molecule]

White solid, mp 48-49 °C (lit.19 mp 47.5 °C), IR (KBr): 2925, 2867, 2854, 1668, 1401, 1365, 940, 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ=7.8(2H, d, J=6.9Hz) 7.79-7.44(8H, m)

1-Indanone (Table 3.4, Entry 4)

![1-Indanone molecule]

¹H NMR (300 MHz, CDCl₃): δ 7.72(d, J = 7.6 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.46(d, J = 7.5 Hz, 1H), 7.46(t, J = 7.2 Hz, 1H), 3.13(t, J = 5.6 Hz, 2H), 2.78(t, J = 6.0 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 207.5, 156.1, 137.4, 135.2, 127.5, 126.9, 124.1, 36.4, 26.1
Acetophenone (Table 3.4, Entry 7)

\[
\text{\includegraphics[width=0.2\textwidth]{acetophenone_structure.png}}
\]
Colourless liquid, (lit. bp 202 °C). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 7.94-7.92\) (d, \(J = 7.8\) Hz, 2H), 7.56-7.51 (t, \(J = 7.35\) Hz, 1H), 7.45-7.40 (t, \(J = 7.5\) Hz, 2H), 2.57 (s, 3H) ppm. IR (KBr) \(v_{\text{max}}\): 1683, 1490, 3066, 3031 and 1691 cm\(^{-1}\).

2-Acetonaphthone (Table 3.4, Entry 6)

\(^1\)H NMR (CDCl\(_3\), 300 MHz): 8.46 (s, 1H), 8.02 (dd, \(J = 8.58, 1.75\) Hz, 1H), 7.94 (d, \(J = 8.58\) Hz, 1H), 7.86 (dd, \(J = 6.20, 5.56\) Hz, 2H), 7.60-7.56 (m, 2H), 2.70 (s, 3H)

4-Methoxyacetophenone (Table 3.4, Entry 10)

\(^1\)H NMR (CDCl\(_3\), 300 MHz): 7.92 (d, \(J = 8.90\) Hz, 2H), 6.92 (d, \(J = 8.90\) Hz, 2H), 3.87 (s, 3H), 2.56 (s, 3H)

Ethyl 4-acetobenzoate (Table 3.4, Entry 11)

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 8.12\) (d, 2H, \(J = 8.4\)), 8.00 (d, 2H, \(J = 8.4\)), 4.40 (q, 2H, \(J = 7.1\)), 2.62 (s, 3H), 1.42 (t, 3H, \(J = 7.2\))

Anthraquinone (Table 3.4, Entry 12): M.P. 285 °C; IR (KBr, cm\(^{-1}\)): 3438, 3072, 1704, 1668, 1624, 1333, 1171; \(^1\)H NMR (300 MHz, CDCl\(_3\)): 7.85-7.86 (d, 4H); 8.27-8.28 (d, 4H); \(^13\)C NMR: 125.6, 132.9, 134.4, 138.1, 182.3, 162.7

Isopropyl ketone (Table 3.4, Entry): IR (KBr cm\(^{-1}\)): 1685, 1467, 1387, 1223, 1160 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 1.23\) (d, \(J = 6.9\) Hz, 6H), 3.55 (sept, \(J = 6.9\) Hz, 1H), 7.47 (t, \(J = 7.3\) Hz, 2H), 7.59 (t, \(J = 7.3\) Hz, 1H), 7.96 (d, \(J = 7.3\) Hz, 2H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 19.1\) (2C), 35.4, 128.2 (2C), 128.4 (2C), 133.1, 136.3, 204.6
Xanthone (Table 3.4, Entry 2): $^1$H-NMR (300 MHz, CDCl$_3$, ppm): $\delta$ 8.32 (dd, $J = 8.4$ Hz, 1.6 Hz, 2H), 7.69 (td, $J = 8.0$ Hz, 1.6 Hz, 2H), 7.42 (d, $J = 8.8$ Hz, 2H), 7.35 (td, $J = 7.4$ Hz, 1.2 Hz, 2H). $^{13}$C-NMR (100 MHz, CDCl$_3$, ppm): $\delta$ 177.4, 156.3, 135.0, 126.9, 124.0, 122.0, 118.1.

Tetralone (Table 3.4, 3): IR (KBr cm$^{-1}$): 2979, 1647, 1600, 1451, 1266, 742, 483; $^1$H NMR (300 MHz, CDCl$_3$); $\delta$ 8.04-8.01 (t, $J = 7.5$ Hz, 1H, ArH), 7.49-7.43 (m, 1H, ArH), 7.32-7.23 (m, 2H, ArH), 2.96 (t, 2H, $J = 6$), 2.65 (t,2H, $J = 6.3$), 2.17-2.09 (m, 2H)